528 Rec'd PCT/PTO 04 OCT 2000

17. X The following fees are submitted:

BASIC NATIONAL FEE [37 CFR 1.492(a)(1)-(5)]:	CALCULATIONS	PTO USE ONLY
_ Search Report has been prepared by the EPO or JPO..... $840.00 _ International preliminary examination fee paid to USPTO [37 CFR 1.482]..... 670.00 __ No International preliminary examination fee paid to USPTO [37 CFR 1.482] but International search fee paid to USPTO [37 CFR 1.445(a)(2)]..... $ 760.00 __ Neither International preliminary examination fee [37 CFR 1.482] nor International search fee [37 CFR 1.445(a)(2)] paid to USPTO.....970.00 X International preliminary examination fee paid to USPTO [37 CFR 1.482] and all claims satisfied provisions of PCT Article 33(1)-(4)..... 96.00		
ENTER APPROPRIATE BASIC FEE AMOUNT:	**$ 96.00**	
Claims — Number filed — Number extra — Rate Total Claims ( ) 07 -20= 0 x $ 18. = Indep. Claims 1 -03= 0 x $ 78 = __ Multiple Dependent Claim(s) (if applicable) + 260. =	$ .00	
TOTAL OF ABOVE CALCULATIONS:	**$ 96.00**	
Surcharge of $130.00 for furnishing the oath or declaration later than [ ] 20 [ ] 30 months from the earliest claimed priority date [37 CFR 1.492(e)]	**$ 0.00**	
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Fee for recording the enclosed assignment [37 CFR 1.21(h)] The assignment must be accompanied by an appropriate cover sheet (PTO-1595) [37 CFR 3.28, 3.31]. $ 40.00 per property +	$ 00.00	
TOTAL FEES ENCLOSED:	**$ 96.00**	
		$ $

X A check in the amount of **$96.00** to cover the above fees in enclosed.

X The Commissioner is hereby authorized to charge the deposit account any other fees required with this submission or to credit any overpayment to Deposit Account No: 04-0838. A duplicate of this form is enclosed.

NOTE: Where an appropriate time limit under 36 CFR 1.494 or 1.495 has not been met, a petition to revive [37 CFR 1.137(a) or (b)] must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

William J. Sapone, Esq.
Coleman Sudol Sapone P.C.
708 Third Avenue
New York, NY 10017

William J. Sapone — Signature — 32,518 Reg. No. — October 4, 2000 Date

Name (Tel. (212) 679-0090)

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail, postage prepaid, in an enveloped addressed to : Assistant Commissioner for Patents, Washington D.C. 20231.

By: _____ Date: 3-1-02

File No. 11496/9-1052

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Candace PERT and Michael RUFF

Serial No. : 09/647749
(based on PCT/US99/07514)

Filed : April 6, 1999

For : SHORT PEPTIDES FOR TREATMENT OF NEUROLOGICAL DEGENERATIVE DISEASES

Assistant Commissioner for Patents
Washington, DC 20231

PRELIMINARY AMENDMENT

Sir:

Prior to the examination of the above-referenced patent application, please amend the application as follows:

IN THE SPECIFICATION

On page 3, line 20, after the formula "Leu-Glu-Ser-Tyr-Thr" insert -- (SEQ. ID NO: 1)--.

On page 3, line 21, after the formula "Ile-Lys-Glu-Tyr-Phe-Thr-Ser" insert -- (SEQ. ID NO: 2)--.

On page 4, line 4 , after the formula "Leu-Glu-Ser-Tyr-Thr" insert --(SEQ. ID NO: 1)--.

On page 4, line 6, after the formula "Ile-Lys-Glu-Tyr-Phe-Thr-Ser" insert --(SEQ. ID NO: 2)--.

On page 4, line 7, after the formula "Leu-Glu-Ser-Tyr-Thr" insert --(SEQ. ID NO: 1)--.

On page 4, line 8, after the formula "Ile-Lys-Glu-Tyr-Phe-Thr-Ser" insert --(SEQ. ID NO: 2)--.

On page 4, line 10, after the formula "Leu-Glu-Ser-Tyr-Thr" insert --(SEQ. ID NO: 1)-- and after the formula "Ile-Lys-Glu-Tyr-Phe-Thr-Ser" insert --(SEQ. ID NO: 2)--.

On page 4, line16, after the formula "Leu-Glu-Ser-Tyr-Thr" insert --(SEQ. ID NO: 1)-- and after the formula "Ile-Lys-Glu-Tyr-Phe-Thr-Ser" insert (SEQ. ID NO: 2)--.

On page 4, line 17, "Leu-Glu-Ser-Tyr-Thr" insert --(SEQ. ID NO: 1)--.

On page 4, line 18 , after the formula "Ile-Lys-Glu-Tyr-Phe-Thr-Ser" insert --(SEQ. ID NO: 2)--.

On page 7, line 7, after "IKEYFTS" insert --(SEQ. ID NO: 2)--.

On page 7, line 7, after "LESYT" insert --(SEQ. ID NO: 1)--.

On page 7, line 8, after "IKEYFTS" insert --(SEQ. ID NO.: 2)--.

On page 7, line 9, after " LESYT" insert --(SEQ. ID NO: 1)--.

On page 7, line 10, after "IKEYF" insert --(SEQ. ID NO: 3)--.

On page 10, after line 2, insert the sequence listing of 2 pages submitted on November 5, 2001.

IN THE ABSTRACT

On page 13, line 7, change" "KEYFTS" to --IKEYFTS, (SEQ. ID NO: 2)--, after "LESYT" insert --(SEQ. ID NO. 1)--.

IN THE CLAIMS

In claim 1, line 2, after the formula "Leu-Glu-Ser-Tyr-Thr" insert --(SEQ. ID NO: 1)--.

In claim 1, line 4, after the formula "Ile-Lys-Glu-Tyr-Phe-Thr-Ser" insert --(SEQ. ID NO: 2)--.

In claim 2, line 3, after the formula "Leu-Glu-Ser-Tyr-Thr" insert --(SEQ. ID NO: 1)--.

In claim 2, line 5, after the formula "Ile-Lys-Glu-Tyr-Phe-Thr-Ser" insert --(SEQ. ID NO: 2)--.

In claim 4, line 3, change "people" to --peptide--.
In claim 4, line 4, after the formula "Leu-Glu-Ser-Tyr-Thr" insert --(SEQ. ID NO: 1)--.

In claim 4, line 5, after the formula, "Ile-Lys-Glu-Tyr-Phe-Thr-Ser" insert --(SEQ. ID NO: 2)--.

In claim 5, line 2, after the formula "Leu-Glu-Ser-Tyr-Thr" insert --(SEQ. ID NO: 1)--.

In claim 6, line 2, after the formula "Ile-Lys-Glu-Tyr-Phe-Thr-Ser" insert --(SEQ. ID NO: 2)--.

REMARKS

Entry of this amendment is solicited to confirm the specification and claims to the sequence listing filed on November 5, 2001. Replacement paragraphs and the claims as amended are enclosed herewith.

No fee is believed required for this amendment. However, if a fee is required, please charge the fee to deposit accout no. 04-0838.

Respectfully submitted,

William J. Sapone
Registration No. 32,518
Attorney for Applicant(s)

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REPLACEMENT PARAGRAPHS FOR THE SPECIFICATION

Page 3, last paragraph:

These and other objects of the present invention are achieved by a pepteiode of the formula

Leu-Glu-Ser-Tyr-Thr (SEQ. ID NO: 1)

or

Ile-Lys-Glu-Tyr-Phe-Thr-Ser (SEQ. ID NO: 2).

Page 4, first 3 full paragraphs:

A method for treating the symptoms associated with neuronal cell death in a person caused by a neurological degenerative disease comprises administering a therapeutically effective amount of a peptide of the formula

Leu-Glu-Ser-Tyr-Thr (SEQ. ID NO: 1)

or

Ile-Lys-Glu-Tyr-Phe-Thr-Ser (SEQ. ID NO: 2)

The invention comprises a peptide of the formula Leu-Glu-Ser-Tyr-Thr (SEQ. ID NO: 1) or Ile-Lys-Glu-Tyr-Phe-Thr-Ser (SEQ. ID NO: 2) or a physiologically acceptable salt thereof. A pharmaceutical composition comprising as a active ingredient at least one peptide of the formula Leu-Glu-Ser-Tyr-Thr (SEQ. ID NO: 1) or Ile-Lys-Glu-Tyr-Phe-Thr-Ser (SEQ. ID NO: 2) or a pharmaceutically acceptable salt thereof, for treating the symptoms caused by neuronal cell loss. The pharmaceutical composition can further comprise a pharmaceutically acceptable carrier.

The invention also includes a method for treating the symptoms caused by a loss of neurons comprising administering to a person suffering from a disease causing neuronal cell loss a therapeutically effective amount of a peptide of formula Leu-Glu-Ser-Tyr-Thr

(SEQ. ID NO: 1) or Ile-Lys-Glu-Tyr-Phe-Thr-Ser (SEQ. ID NO: 2) or pharmaceutically acceptable salt thereof. The method can comprise either the formula Leu-Glu-Ser-Tyr-Thr (SEQ. ID NO: 1) or Ile-Lys-Glu-Tyr-Phe-Thr-Ser (SEQ. ID NO: 2). According to the method, the peptide is administered by oral, intranasal, buccal, parenteral, topical or rectal administration.

Page 7, first full paragraph:

When the peptides were added to primary cultures of mixed rat neurons/glia, together with 1 pM gp120 (RF isolate), which by itself killed about half the neurons in the dish (Fig. 1), neuronal death could be inhibited. In a dose-dependent fashion, significant increases in cell counts were observed from cultures treated with gp120 alone, with IKEYFTS (SEQ. ID NO: 2) and LESYT (SEQ. ID NO: 1) preventing neuronal loss caused by gpl20. The peptide IKEYFTS (SEQ. ID NO: 2) had an EC50 of 100 nM and was fully protective at 10μM, while LESYT (SEQ. ID NO: 1) was partially protective at 10μM. Specificity is shown in that the shorter pentapeptide IKEYF (SEQ. ID NO: 3) was inactive. The dotted line in Figure 1 represents the mean number of neurons in control cultures.

THE CLAIMS AS AMENDED

Claim 1. A peptide of the formula

Leu-Glu-Ser-Tyr-Thr (SEQ. ID NO: 1)

or

Ile-Lys-Glu-Tyr-Phe-Thr-Ser (SEQ. ID NO: 2)

or a physiologically acceptable salt thereof.

Claim 2. A pharmaceutical composition comprising as an active ingredient at least

one peptide of the formula

Leu-Glu-Ser-Tyr-Thr (SEQ. ID NO: 1)

or

Ile-Lys-Glu-Tyr-Phe-Thr-Ser (SEQ. ID NO: 2)

or a pharmaceutically acceptable salt thereof, for treating the symptoms caused by neronal cell loss.

Claim 4. A method for treating the symptoms caused by a loss of neurons comprising administering to a person suffering from a disease causing neuronal cell loss a therapeutically effective amount of a peptide of formula

Leu-Glu-Ser-Tyr-Thr (SEQ. ID NO: 1)

or

Ile-Lys-Glu-Tyr-Phe-Thr-Ser (SEQ. ID NO: 2)

or a pharmaceutically acceptable salt thereof.

Claim 5. The method of claim 4 wherein the formula is

Leu-Glu-Ser-Tyr-Thr (SEQ. ID NO: 1).

Claim 6. The method of claim 4 wherein the formula is

Ile-Lys-Glu-Tyr-Phe-Thr-Ser (SEQ. ID NO: 2)

REPLACEMENT ABSTRACT

The HIV-1 envelope protein gpl20 is toxic to rodent and human neurons by indirect mechanisms requiring accessory glial cells. Chemokines are known to block gpl20 interactions with chemokine receptors on T cells, macrophages, and microglia, thereby preventing viral infection. Gpl20-induced neuronal killing in rat hippocampal cultures was partially or completely prevented by a specific short peptides related to chemokines, specifically IKEYFTS (SEQ. ID NO: 2) and LESYT (SEQ. ID NO: 1). These peptides thus have use in the treatment of neurological degenerative diseases having symptoms associated with neuronal cell death.

SHORT PEPTIDES FOR TREATMENT OF NEUROLOGICAL DEGENERATIVE DISEASES

TECHNICAL FIELD

This invention is directed to synthetically produced short peptide sequences which inhibit HIV-1 gpl20 induced neuronal cell death, for use in preventing neurological deterioration in patients suffering from AIDS as well as other neurological degenerative diseases.

BACKGROUND

Among the symptoms and conditions associated with HIV infection (AIDS) are specific neurological conditions which can be termed "neuro-AIDS".

Neuro-AIDS, whose incidence and severity appears to be increasing, can manifest itself in many forms including encephalopathies, neuropathies, memory loss, dementia, depression, psychosis and opportunistic infections. One explanation for AIDS associated neuropathologies, which can include infiltration of infected immune cells, white matter aberrations, reduced dendritic and axonal arborization, and neuronal loss is that dissociated HIV envelop protein, gpl20, which has been shown to be secreted abundantly by infected macrophages and is present in plasma and CSF, contributes to pathogenesis via receptor-mediated interactions with various shared cell surface receptors on brain and immune cells.

There is growing evidence that neurotoxicity and infectivity associated with HIV have distinctive attributes suggesting divergence of mechanism. In particular, HIV infection does not occur in rodents and does not require signaling, while the

biological activities associated with the envelope protein can be demonstrated in both human and rodent cells and requires signaling. The neurotoxic action of HIV-1 envelope protein gpl20 is potent and requires the presence of glial cells, which may then secrete neurotoxic products or cytokines. In rodents, intraventricularly administered gpl20 produces endocrine abnormalities.

The neuropeptide vasoactive intestinal peptide (VIP), as well as homologous short (5-8 residues) peptides derived from the gpl20 V2 region derived peptides (8-10) are inhibitors of gpl20 neurotoxicity. In neonatal rats, delayed behavioral milestones and abnormal neuronal dearborization produced by administration of nanogram quantities of gpl20 are also prevented by VIP (II) and gpl20 V2-region derived peptide T ("DAPTA"). In the same study, toxic fragments of gpl20 were recovered from treated animals, suggesting that some of the neural damage is attributable to proteolytic products of the HIV envelope.

Alzheimers' Disease or dementia is believed to be caused by the deterioration of the cholinergic neurons in the basal forebrain. VIP is co-localized with cholinergic neurons in the basal forebrain and is believed to maintain neuronal survival. In a proposed secondary phase of Alzheimers' disease, endogenous neurons of the cortex of various different chemical types degenerate following deprivation of their vasoactive intestinal polypeptide neuronal growth factor once contained in the cholinergic endings.

In U.S. Patent No. 5,567,682, short chain peptides, specifically peptide T and related analogs, are described for treating the symptoms of Alzheimers' disease by reducing or halting a loss of neurons. Similarly, these peptides are described as being useful in inhibiting HIV-1 binding to T4 cell receptors (U.S. Patent No. 5,276,016).

Recent discoveries show that HIV gpl20 uses a number of chemokine co-receptors, in conjunction with CD4, to allow viral entry of target cells. Moreover, various gpl20's can block binding of specific chemokine ligands with the CCR5 receptor. Chemokine receptors, first characterized on activated immune cells, have been shown to also be present on cerebellar neuronal processes, differentiated human neuronal lines, and both microglial cells and astrocytes in human brain cultures. Thus the inventors sought to identify novel short chemokine peptides which would be antagonists of gpl20-mediated neurotoxicity and resultant neuronal degeneration and thereby provide therapeutic benefits in patients suffering from HIV infection, or other inflammatory neurological diseases such as multiple sclerosis, tropical spastic paraparesis, and Alzheimers, to cite some.

SUMMARY OF THE INVENTION

It is an object of the present invention to provide peptides and a method for treating diseases having symptoms caused by neuronal cell death caused by HIV, MS, Alzheimers' Disease, PML, and Tropical Spastic Paraparesis, among others.

It is another object to provide a pharmaceutical composition having a peptide as an active agent for reducing or inhibiting neuronal cell loss.

These and other objects of the present invention are achieved by a peptide of the formula

Leu-Glu-Ser-Tyr-Thr

or

Ile-Lys-Glu-Tyr-Phe-Thr-Ser

A method for treating the symptoms associated with neuronal cell death in a person caused by a neurological degenerative disease comprises administering a therapeutically effective amount of a peptide of the formula

Leu-Glu-Ser-Tyr-Thr

or

Ile-Lys-Glu-Tyr-Phe-Thr-Ser

The invention comprises a peptide of the formula Leu-Glu-Ser-Tyr-Thr or Ile-Lys-Glu-Tyr-Phe-Thr-Ser or a physiologically acceptable salt thereof. A pharmaceutical composition comprising as an active ingredient at least one peptide of the formula Leu-Glu-Ser-Tyr-Thr or Ile-Lys-Glu-Tyr-Phe-Thr-Ser or a pharmaceutically acceptable salt thereof, for treating the symptoms caused by neuronal cell loss. The pharmaceutical composition can further comprise a pharmaceutically acceptable carrier.

The invention also includes a method for treating the symptoms caused by a loss of neurons comprising administering to a person suffering from a disease causing neuronal cell loss a therapeutically effective amount of a people of formula Leu-Glu-Ser-Tyr-Thr or Ile-Lys-Glu-Tyr-Phe-Thr-Ser or a pharmaceutically acceptable salt thereof. The method can comprise either the formula Leu-Glu-Ser-Tyr-Thr or Ile-Lys-Glu-Tyr-Phe-Thr-Ser. According to the method, the peptide is administered by oral, intranasal, buccal, parenteral, topical or rectal administration.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows neuronal cell survival with reference to peptide concentration.

DETAILED DESCRIPTION OF THE INVENTION

Materials: A gpl20 isolate RFII was obtained from Dr. P.Nara, NCI, NIH. All of the gpl20's are purified, >95% homogeneous and previously tested for neurotoxicity with cultured neurons and were used at lpM final concentration in cultures of neurons. Peptides of the formula Ile-Lys-Glu-Tyr-Phe-Thr-Ser, Ile-Lys-Glu-Tyr-Phe, and Leu-Glu-Ser-Tyr-Thr were obtained from Peninsula Labs, CA. and synthesized by solid-phase Merrifield methods and purified to greater than 95% homogeneity by two HPLC methods and structure confirmed by MASS Spectroscopy Analysis.

Neuronal cell culture: Dissociated hippocampal cultures are prepared from neonatal (day 2) rat cortex and hippocampus by known methods. Sterilely dissected brain tissue is minced and treated with 0.125% trypsin for 30 minutes then gently triturated with fire-polished Pasteur pipes and plated in six-well trays ($35mm^2$) at low density (5O,000 cells/$35mm^2$ dish) upon confluent layers of astrocytes in medium containing D-MEM, penicillin (25 U/ml), streptomycin (25 mg/ml), D-glucose (0.6%), and 10% heat-inactivated fetal calf serum (HyClone Laboratories), supplemented with insulin, transferrin, selenium, corticosterone, and triiodothyronine. Medium is changed after 3 days. At 6 days, half the medium is exchanged for fresh medium. The astrocyte feeder layers were prepared from the cortexes of neonatal rats following dissection and trituration. Plating was 2.5 $X10^2$ cells per well. Feeder layers were grown in Eagles's minimal essential medium (Formula No. 82-0234DJ, Gibco) with 10% fetal calf serum until confluent (7-14 days). With this medium the feeder cultures were free of neurons and consisted of flat cells that were stained by antibodies to glial fibrillary acidic protein, a standard immunocytochemical marker for astroglia. When hippocampal or cortical

cells were added to the confluent feeder layer, the medium was changed to the following composition: 5% horse serum and MEM supplement with defined medium components. The hippocampal or cortical cultures were treated with 5'-fluoro-2'-deoxyuridine (l5ug/ml plus uridine, 35ug/ml) to suppress the overgrowth of background cells and allow the establishment of neurons. The neurons in these cultures are post-mitotic. The neuronal cultures were allowed to grow for 1 week prior to the beginning of the experimental period. Before treating the cultures, a complete change of medium was given.

Neuronal survival assay: GP120's, with or without added peptides, were diluted in phosphate buffered saline and added to the cultures, which were treated only once for a four day period. At termination, cultures were fixed with glutaraldehyde as previously described. At the end of the test period, neuronal survival was assessed by immunohistochemical detection of neuron-specific enolase positive cells (neurons). Cultures were counted in a blinded fashion without knowledge of sample treatment in 40 fields at pre-determined coordinate locations. The total area counted is 50 mm^2 . Each value reported is the mean $\pm$ the standard error of 3-4 determinations. Control (saline treated) wells from these cultures have 395 $\pm$ 20 neurons. Statistical comparisons between experimental and control culture neuronal cell counts are via analysis of variance with the Student-Newman-Kuels multiple comparison of means test.

Results

Effects of Short Chemokine Derived Peptides on GPI20-Mediated Neurotoxicity

When the peptides were added to primary cultures of mixed rat neurons/glia, together with 1 pM gpl20 (RF isolate), which by itself killed about half of the neurons in the dish (Fig. 1), neuronal death could be inhibited. In a dose-dependent fashion, significant increases in cell counts were observed from cultures treated with gp120 alone, with IKEYFTS and LESYT preventing neuronal loss caused by gpl20. The peptide IKEYFTS had an EC50 of IOO nM and was fully protective at IOuM, while LESYT was partially protective at IOuM. Specificity is shown in that the shorter pentapeptide IKEYF was inactive. The dotted line in Figure 1 represents the mean number of neurons in control cultures.

The peptides also supported the viability of neurons in the absence of added gpl20 and thus acted as survival factors. The results thereby identify novel, short chemokine related peptides which have significant neuroprotective activity against gpl20 neurotoxicity as well as promote neuronal survival and which therefore may be treatments for AIDS and other neurodegenerative diseases which includes, but is not limited to conditions like Alzheimers, multiple sclerosis, tropical paraparesis, PML and neuropathies of various etiologies including diseases resulting from or relating to HTLV-1 infection, to cite some examples.

The peptides may be administered in suitable carriers by various routes including oral, buccal, iv, rectal, nasal, with effective doses from 0.01 mg to 1000 mgs per day, preferably from 0.2 to 10 mg per day for a 70 kg person.

The active compounds of the invention may exist as physiologically

acceptable salts of the peptides.

The compounds of the invention may be beneficially modified by methods known to enhance passage of molecules across the blood-brain barrier. Acetylation has proven to be especially useful for enhancing binding activity of the peptide. The terminal amino and carboxy sites are particularly preferred sites for modification.

The peptides of this invention may also be modified in a constraining conformation to provide improved stability and oral availability.

Unless otherwise indicated the amino acids are, of course, the natural form of L-stereoisomers.

The peptides that are to be administered intranasally in accordance with the invention may be produced by conventional methods of peptide synthesis. Both solid phase and liquid phase methods, as well as other methods e.g., enzymatic methods, may be used. We have found the solid phase method of Merrifield to be particularly convenient. In this process the peptide is synthesized in a stepwise manner while the carboxy end of the chain is covalently attached to an insoluble support. During the intermediate synthetic stages the peptide remains in the solid phase and therefore can conveniently manipulated. The solid support is a chloromethylated styrene-divinylbenzene copolymer.

As an aspect of the invention, therefore, we provide a pharmaceutical compositions comprising a peptide compound of the invention in association with pharmaceutically acceptable carrier or excipient, adapted for use in human or veterinary medicine. Such compositions may be presented for use in a conventional manner in admixture with one or more physiologically acceptable carriers of

excipient. The compositions may optionally further contain one or more other therapeutic agents which may, if desired, be a different antiviral agent.

Thus, the peptides according to the invention may be formulated for oral, intranasal, buccal, parenteral, topical or rectal administration.

In particular, the peptides according to the invention may be formulated for injection or for infusion and may be presented in unit dose form in ampoules or in multidose containers with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g., sterile, pyrogen-free water, before use. In a particularly preferred embodiment, the active ingredient may be administered intranasally, preferably in more than one daily application.

The pharmaceutical compositions according to the invention may also contain other active ingredients such as antimicrobial agents, or preservatives.

A further aspect of this invention relates to vaccine preparations containing a peptide according to the invention, to provide protection against viral infection. The vaccine will contain an effective immunogenic amount of peptide, e.g. 1μg to 20 mg/kg of host, optionally conjugated to a protein such as human serum albumin, in a suitable vehicle, e.g. sterile water, saline or buffered saline. Adjuvants may be employed, such as aluminum hydroxide gel. Administration may be by injection, e.g. intramuscularly, interperitoneally, subcutaneously or intravenously. Administration may take place once or at a plurality of times, e.g. at 1-4 week intervals.

Antigenic sequences from crab as well as proteins from other invertebrates can also be added to the peptides of the invention to promote antigenicity.

IN THE CLAIMS

Claim 1. A peptide of the formula

Leu-Glu-Ser-Tyr-Thr

or

Ile-Lys-Glu-Tyr-Phe-Thr-Ser

or a physiologically acceptable salt thereof.

Claim 2. A pharmaceutical composition comprising as an active ingredient at least one peptide of the formula

Leu-Glu-Ser-Tyr-Thr

or

Ile-Lys-Glu-Tyr-Phe-Thr-Ser

or a pharmaceutically acceptable salt thereof, for treating the symptoms caused by neuronal cell loss.

Claim 3. The pharmaceutical composition of claim 2 further comprising a pharmaceutically acceptable carrier.

Claim 4. A method for treating the symptoms caused by a loss of neurons comprising administering to a person suffering from a disease causing neuronal cell loss a therapeutically effective amount of a people of formula

Leu-Glu-Ser-Tyr-Thr

or Ile-Lys-Glu-Tyr-Phe-Thr-Ser

or a pharmaceutically acceptable salt thereof.

Claim 5. The method of claim 4 wherein the formula is

Leu-Glu-Ser-Tyr-Thr.

Claim 6. There method of claim 4 wherein the formula is

Ile-Lys-Glu-Tyr-Phe-Thr-Ser.

Claim 7. The method of claim 4, wherein the peptide is administered by oral, intranasal, buccal, parenteral, topical or rectal administration.

ABSTRACT

The HIV-I envelope protein gpl20 is toxic to rodent and human neurons by indirect mechanisms requiring accessory glial cells. Chemokines are known to block gpl20 interactions with chemokine receptors on T cells, macrophages, and microglia, thereby preventing viral infection. Gpl20-induced neuronal killing in rat hippocampal cultures was partially or completely prevented by specific short peptides related to chemokines, specifically KEYFTS and LESYT. These peptides thus have use in the treatment of neurological degenerative diseases having symptoms associated with neuronal cell death.

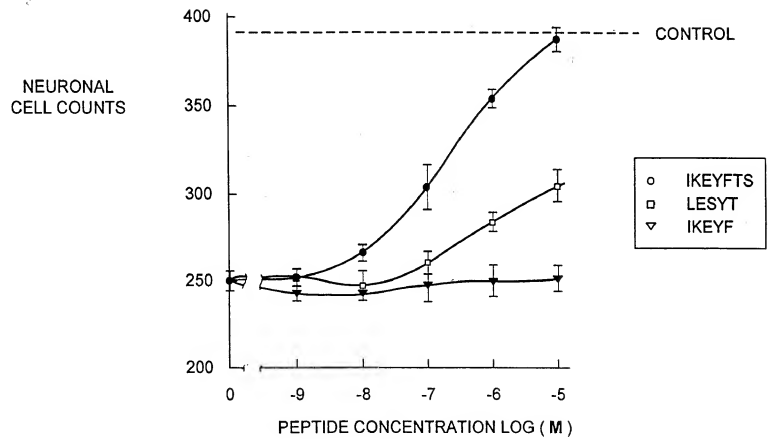

FIG. 1

Docket No.: 11496/9-105

09647749 .061201

DECLARATION FOR PATENT APPLICATION

As a below-named inventor(s), I (we) hereby declare that:

My (our) residence(s), post office address(es) and citizenship(s) is (are) the same as stated below next to my (our) name(s).

I (we) believe I am (we are) an original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled: **SHORT PEPTIDES FOR TREATMENT OF NEUROLOGICAL DEGENERATIVE DISEASES**

the specification of which is attached hereto unless the following box is checked:

[X] was filed on October 4, 2000 as United States Application Number 09/647749
based on PCT International Application Number PCT/US99/07514 filed April 6, 1999
and was amended on _____ (if applicable).

I (we) hereby state that I (we) have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I (we) acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, §1.56.

I (we) hereby claim foreign priority benefits under Title 35, United States Code, §119(a)-(d) of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Prior Foreign Application(s):			Priority YES	Claimed: NO
(Number)	(Country)	(Day/Month/Year)		

I (we) hereby claim the benefit under Title 35, United States Code, §119(e) of any United States provisional application(s) listed below:

60/080,836 — **6 April 1998**

(Application Number) (Filing Date)

I (we) hereby claim the benefit under Title 35, United States Code, § 120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, § 112, I (we) acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulation, §1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

(Application Serial No.)	(Filing date)	(STATUS-patented, pending, abandoned)

526 Rec'd PCT/PTO 04 OCT 2000

Attorney's Docket No.	: **11496/9-1052**
U.S. Application No.	: To be assigned
Filed	: Herewith - October 4, 2000
Applicant(s)	: Candace PERT and Michael RUFF
International Application No.	: **PCT/US99/07514**
International Filing Date	: **April 6, 1999 (06 April 1999)**
Priority Date Claimed	: **April 6, 1998 (06 April 1998) (US Prov. no. 60/080,836)**
Title of Invention	: **SHORT PEPTIDES FOR TREATMENT OF NEUROLOGICAL DEGENERATIVE DISEASES**

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. X This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. _ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. _ This express request to begin national examination procedures [35 U.S.C. 371 (f)] at any time rather than delay examination until the expiration of the applicable time limit set forth in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. X A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. X A copy of the International Application as filed [35 U.S.C. 371(c)(2)]
   a) X is transmitted herewith (required only if not transmitted by the International Bureau)
   b) _ has been transmitted by the international Bureau
   c) _ is not required, as the application was filed in the United States Receiving Office (RO/US)
6. _ A translation of the International Application into English [35 U.S.C. 371(c)(2)]
7. _ Amendments to the claims of the International Application under PCT Article 19 [35 U.S.C. 371(c)(3)]
   a) _ are transmitted herewith (required only if not transmitted by the International Bureau)
   b) _ have been transmitted by the International Bureau
   c) _ have not been made; however, the time limit for making such amendments has **NOT** expired.
   d) _ have not been made and will not be made
8. _ A translation of the amendments to the claims under PCT Article 19 [35 U.S.C. 371(c)(3)]
9. _ An oath or declaration of the inventor(s) [35 U.S.C. 371(c)(4)]
10. _ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 [35 U.S.C. 371(c)(5)]

Items 11. to 16. below concern other document(s) or information included:

11. ___ An Information Disclosure Statement under 37 C.F.R. 1.97 and 1.98
12. ___ An Assignment document for recording. A separate cover sheet (PTO-1595) in compliance with 37 CFR 3.28 and 3.31 are included.
13. _ A **FIRST** preliminary amendment
    _ A **SECOND** or **SUBSEQUENT** preliminary amendment
14. _ A substitute specification
15. _ A change of power of attorney and/or address letter
16. X (other items or information) **PCT/IPEA/409, PCT PUB. NO WO/99/51254;**

EXPRESS MAIL No.: **EL020806970 US** Deposited: **October 4, 2000**
I hereby certify that this correspondence is being deposited with the United States Postal Service Express mail under 37 CFR 1.10 on the date indicated above and is addressed to: BOX PCT, Commissioner for Patents, Washington, DC 20231.

Susan Simon
Susan Simon

Date: **October 4, 2000**

Docket No.: 11496/9-1052

DECLARATION FOR PATENT APPLICATION

I (we) hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith and to act in accordance with the instructions from :

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I (we) hereby declare that all statements made herein of my (our) own knowledge are true, and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

1-00

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2-00

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Inventor's signature: Michael R Ruff Date: 6/7/01

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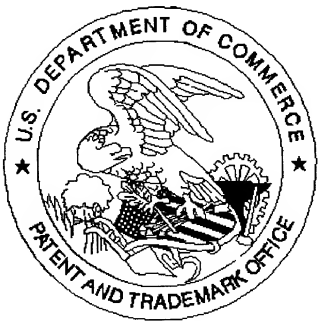

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